

Thimerosal



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Summary

- Thimerosal is a preservative with ethylmercury.
- Not as much is known about ethylmercury as methylmercury, but toxicity appears less and elimination from body after vaccine appears better.
- Bureau of Health moved in 1999 to provide only thimerosal-free vaccines whenever possible.
- Recommended childhood vaccines in Maine have been virtually thimerosal-free for several years.
- Some vaccines that are primarily for older children and adults are not available yet without thimerosal.
- Thimerosal-containing vaccines may be necessary in epidemics and in other situations where multi-use vials are needed.



Summary

- There are no known long-term risks of thimerosal when given in vaccine, but there are very known risks of non-immunization or immunization with bacterial contamination.
- Major public concern with effects of thimerosal-containing vaccines (TCV) is autism. Six epidemiological studies examining TCV and autism from Denmark, Sweden, U.K., and U.S. show no association between TCVs and autism.
- When thimerosal was discontinued (Denmark and Sweden), autism did not decline.
- There is a great need for broad research on the causes and treatment of autism.



What is Thimerosal?

- Is a preservative containing ~49% ethylmercury;
- Has been used in vaccines and other pharmaceuticals (ophthalmic and nasal products) since the 1930's;
- Assures non-contamination from bacteria;
- Is necessary in most multi-dose vials;
- When not used, single dose vials are necessary;
- Before its use, reports of fatal and life-threatening bacterial infections from vaccine injections.



1999

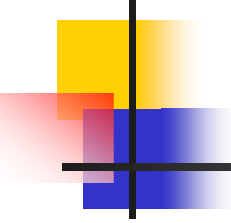
- FDA asked by Congress in 1997 to study exposures to mercury.
- Summer 1999, FDA announced infants might be exposed to cumulative doses of ethylmercury through thimerosal in vaccines that exceeded guidelines established for methylmercury by EPA and ATSDR (for small infants only).
- FDA and WHO guidelines not exceeded.
- Two studies suggested linkage between childhood vaccines and autism - one focused on MMR and one on the rise of infant vaccines in the 1990's, along with a rise in autism.



1999

- The Bureau of Health started in July, 1999 to provide thimerosal-free vaccine whenever possible.
- Nationally, by March 2001, all formulations of vaccines for 6 years and younger became available thimerosal-free, with last expiration dates of TCV (thimerosal-containing vaccine) in 2002.

Exposure to Mercury from Vaccines 1999 vs. 2005



	<u>1999 Max. Mercury</u> (μg)		<u>2005 Max. Mercury</u> (μg)
Infants <6 months	188	→	Trace ($\ll 2.4$)
Children <2 years	275	→	Trace ($\ll 2.4$)



What is Mercury?

- Is a heavy metal = Hg (as is Lead = Pb);
- Can bind to proteins;
- Central nervous system and kidney are primary sites of toxicity;
- Children are most susceptible to toxicity (low body weight and developing nervous system);
- Three common types of mercury: Elemental, Inorganic, and Organic (methyl and ethyl);
- The types of mercury differ in toxicity and toxicokinetics (they are not equal).



Elemental Mercury

- Used in thermometers, barometers, dental amalgam
- Well-absorbed if inhaled
- Poorly absorbed if ingested or handled.



Organic Mercury - Methylmercury

- Found in fish -> Bureau of Health's Fish Consumption Advisories.
- Pollution releases elemental mercury from smokestack precipitates and forms organic mercury once in watersheds, accumulating in fish.
- People eating some fresh fish ingest methylmercury, which is readily absorbed and can cross the blood-brain barrier.
- One can of white tuna per week -> 6-8 micrograms methylmercury per day (half for light canned tuna).



Organic Mercury - Ethylmercury

- In thimerosal.
- Limited toxicological data on this type of mercury.
- Studies indicate:
 - Thimerosal accumulates in the blood and brain to a much lower degree than methylmercury.
 - Ethylmercury is eliminated from infants rapidly from blood via stools after TCV (Thimerosal-Containing Vaccine) is administered.



2004 Institute of Medicine (IOM) Report

- Studied possible relationship between thimerosal in vaccines and autism.
- “The committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.”



Autism – What Is It?

- Complex set of developmental disorders with impairments in social interaction, verbal and non-verbal communication, repetitive patterns of behavior.
- PDD (Pervasive Developmental Disorders) and ASD (Autistic Spectrum Disorder) are often used interchangeably with “Autism”, but refer to a broader group of disorders, including autistic disorder, Asperger’s syndrome, Rett’s syndrome, and childhood disintegrative disorder.
- Different forms of Autism:
 - Early Onset type (majority of autism), with symptoms apparent on retrospective infant videos, but diagnosis usually made at 2-3 years of age;
 - Regressive type (much rarer), with normal development followed by failure to progress or regression in development.



Autism – How Common Is It?

- Prevalence ~10/10,000, though some studies indicate this is higher and increasing.
- CA study showed rates increased 5.8 to 14.9 per 10,000 from 1987 to 1994 birth cohorts, using children registered in CA Developmental Services system.
- However, consistent case definitions and other methodological challenges make assessing trends difficult.
- Numbers do not reflect large impact of autism on families and society.



Maine Data on Children with Autism Accessing Services

Children Ages 3-20 with Autism Served by Maine DOE

2001	712
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2004	1,255
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Children Ages 3-5 with Autism Served by Maine CDS

2000	105
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2003	203
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These datasets do not include children with multiple diagnoses, some of whom have autism.



Autism – What Are the Possible Causes?

- **Genetics** – plays a role, since high rates among twins (90% among identical twins) and other siblings (50-100 higher rates among siblings).
- **Early Gestational Insults** – some pathophysiological evidence for this.
- **Immune Dysregulation** – some evidence shows associated findings, but unclear if they are part of the syndrome or a cause of it.
- **Abnormal Mercury Metabolism** – autism not shown to be associated with mercury exposure.
- **Thimerosal Neurotoxin Effects** – no evidence of this from epidemiological studies.
- **Pharmacogenetics** – genetic susceptibility to pharmacological effects, would be difficult to detect in epidemiological studies.



Autism – Challenges to Research

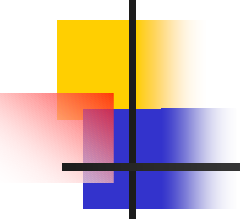
- Uncertain prevalence and incidence trends
- Changing case definitions
- Little knowledge of natural history of autism
- No strong biological model for autism
- Lack of diagnostic biomarkers
- Limited understanding of associated features – immune and gastrointestinal

**Need more research on causes
and treatment of autism!!**



MMR Vaccine and Autism

- 1998 Wakefield Study retrospective case series of 12 children with autism
- Retrospective interviews – association of MMR with onset of symptoms in 8 children
- Study stated it showed no proven association
- MMR is live virus vaccine – no thimerosal
- Since 1998, numerous studies published, all showing no association between MMR and autism
- 2004 IOM Report: “favors rejection of a causal relationship between the MMR vaccine and autism”



Studies Regarding Thimerosal-Containing Vaccines (TCV) and Autism



Hviid 2003 Danish Study

- No thimerosal in childhood vaccines in Denmark after 1992. Pertussis vaccine was the only childhood TCV, and only from 1961-1992.
- Study compared rates of autism and other related conditions in 467,450 Danish children who received TCV with those who received thimerosal-free vaccine.
- No association between TCV and autism, between TCV and autistic spectrum disorders, and no dose response association between autism and amounts of ethylmercury exposed to via thimerosal.



Verstraeten 2003 U.S. Vaccine Safety Datalink (VSD) Study

- Retrospective cohort study from databases of two HMOs.
- VSD links CDC and HMO health information for 8 HMOs nationwide.
- No association between TCV ethylmercury doses and autism or neurodevelopmental disorders.
- Controversies raised re: preliminary findings of the relative risk of autism showing a positive but non-significant association in earlier analyses versus the relative risk showing no association in final published study. IOM reviewed the changes between preliminary results and final study, and found routine expected changes such as updating datasets with longer follow-up information.



Madsen 2003 Danish Study

- Ecological study on Danes with autism diagnosed 1971-2000 (thimerosal in Danish vaccines 1961-1992 at fairly steady doses).
- No increased incidence of autism during time when TCV used in Denmark up to 1990. Autism then increased throughout 1990s-2000s, on par with U.S. increases, even after thimerosal was discontinued.
- No decrease in autism after thimerosal removed from vaccines.



Stehr-Green 2003 Sweden Study

- Ecological study on incidence of autism among Swedes born 1980-1996.
- No TCV in Sweden after 1992.
- No association between TCV and autism incidence, which increased in 1990s, and continued to increase after thimerosal was eliminated from vaccines.
- No decrease in autism after thimerosal was eliminated.



Stehr-Green 2003 Danish Study

- Ecological study comparing incidence of autism among Danes per year 1983-2000 to TCV used.
- TCV at steady levels 1970-1991, then eliminated 1991-1993.
- Autism incidence steady <1990, then increased throughout 1990s.
- No association between TCV and autism incidence, which increased after thimerosal was eliminated from vaccines. No decrease in autism after thimerosal was eliminated.



Miller 2004 U.K.

- Controlled observational study on autism and other neurodevelopmental disorders and TCVs using U.K. General Practice Research Database (GPRD), which is similar to U.S.' VSD, and covers 5.7% of the population.
- Only TCV in U.K. was DPT and DT vaccines.
- Over 100,000 children born 1988-1997 included in the study.
- No dose response to thimerosal related to autism and other disorders seen.



Geier & Geier US 2003 and 2004 Studies Vaccine Distribution and DOE Data

- These studies compared distributed vaccine doses in U.S. and numbers of children with autism reported to U.S. Department of Education (DOE) for several birth cohorts in 1980s and 1990s.
- Concluded autism increased 6 times 1980s to 1990s.
- Reported a dose-response of thimerosal to autism.



Serious Flaws of Geier & Geier Studies

- **Vaccine Data:** These studies used number of doses of vaccine distributed nationwide per year (not doses administered) used as data source. These data do not indicate individual children's thimerosal exposure (necessary to determine dose response) nor vaccine administered per age group.
- **DOE Data:** Show the number of all school children served for autism at a point in time, but inadequate as a proxy for birth-cohort prevalence. States use different definitions for autism to determine eligibility for services. Nationally, children with autism in this database were reported in a separate disability category starting in 1990.



Serious Flaws of Geier & Geier Studies

- Analytical methods reported in these studies omitted many details such as how calculations were made and types of analyses done.
- IOM found these studies to be “un-interpretable, and therefore, non-contributory with respect to causality”.



Geier & Geier US 2003 DTaP and VAERS

- Three 2003 ecological studies compared U.S. use of DTaP thimerosal-free vaccine versus DTaP TCV with rates of autism and other adverse outcomes.
- Concluded: dose responses between thimerosal in DTaP TCV and reports of autism, speech disorders, as well as dose responses between TCV and other neurodevelopmental disorders compared with other reported effects such as fevers.



These 3 studies found by IOM to be un-interpretable

- Used VAERS = Vaccine Adverse Events Reporting System, an FDA and CDC self-reporting system. Is good as an “early warning system” to detect rare events, but inadequate to analyze association, since no control group for comparison, no ability to determine denominators, and biased reporting.
- Used distributed vaccine data as proxy for administered vaccine amounts rather than immunization coverage rates for birth cohorts.
- Much of the data analysis was missing and/or applied incorrectly.



Summary of Studies on TCV and Autism

- Epidemiological studies examining TCVs and autism, including three controlled observational studies from Denmark, U.K. and U.S. and two uncontrolled observational studies from Denmark and Sweden consistently provide evidence of no association between TCVs and autism.
- In countries where thimerosal was discontinued, autism did not decline after its elimination, and actually increased, on par with increases seen in the U.S.
- Therefore, the IOM concluded in 2004: “the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism”.



Vaccine Benefits Are Proven

Measles

- Pre-vaccine 1963 – measles caused an estimated 4,000 to 8,000 deaths and 4,000 cases of encephalitis annually in the U.S.
- 2003 – 42 measles cases reported in the U.S.

Polio

- Prevaccine 1955 – polio killed or disabled thousands of children and young adults every year. Even going to the beach during epidemics was dangerous.
- 2005 – polio infections eliminated from Western Hemisphere for years.

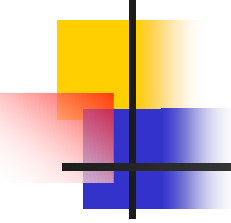
Hemophilus B - HiB

- Pre-vaccine 1980s – most common cause of fatal bacterial meningitis in children.
- 2005 – no cases of HiB meningitis in Maine in over 10 years.



Status of Thimerosal in Vaccines

- Thimerosal use in vaccines has diminished greatly since 1999, especially in childhood vaccines.
- The maximum amount of ethylmercury an infant in the U.S. exposed to through routine childhood immunizations was 188 micrograms in 1999, and is now << 2.4 micrograms.
- All routine childhood vaccines provided by the Bureau of Health are now considered free of thimerosal except for trace amounts found in 2 of them.

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- DTaP, and occasionally Hepatitis B can contain a trace of thimerosal that is left over from the manufacturing process.
 - Thimerosal-free preservative-free pediatric influenza vaccine is now available for the 2005 flu season. Maine HHS' Public Health has ordered over 24,000 doses, enough for all children under 3 years old who are recommended to have flu vaccine.
 - Adult Influenza Vaccine, when given as a half-dose to children (over 2 years old), contains 12.5 micrograms of ethylmercury.
 - CDC is proposing to add information on thimerosal to Vaccine Information Statements.



Summary

- Thimerosal use has diminished greatly since 1999 (with ethylmercury exposure from 188 micrograms to a maximum of <<2.4 micrograms from routine infant immunizations).
- Childhood vaccines in Maine have been virtually thimerosal-free for several years.
- There are no known long-term risks of thimerosal when given in vaccines, but there are very known risks of non-immunization.